Bioorganic & Medicinal Chemistry Letters 27 (2017) 4558–4563

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and biological evaluation of the natural product komaroviquinone and related compounds aiming at a potential therapeutic lead compound for high-risk multiple myeloma

Yutaka Suto [a,*], Mariko Sato [b], Kota Fujimori [b], Shotaro Kitabatake [b], Mikio Okayama [b,c], Daiju Ichikawa [b], Maiko Matsushita [b], Noriyuki Yamagiwa [a], Genji Iwasaki [a], Fumiyuki Kiuchi [d], Yutaka Hattori [b]

[a] Faculty of Pharmacy, Takasaki University of Health and Welfare, Gunma 370-0033, Japan
[b] Clinical Physiology & Therapeutics, Keio University Faculty of Pharmacy, Tokyo 105-8512, Japan
[c] Division of Hematology, Department of Internal Medicine, Keio University, Tokyo 160-8582, Japan
[d] Keio University Faculty of Pharmacy, Natural Medicines, Tokyo 105-8512, Japan

ARTICLE INFO

Article history:
Received 25 May 2017
Revised 22 August 2017
Accepted 25 August 2017
Available online 30 August 2017

Keywords:
Multiple myeloma
Antitumor reagent
Natural product

ABSTRACT

Alternatives of treatments for multiple myeloma (MM) have become increasingly available with the advent of new drugs such as proteasome inhibitors, thalidomide derivatives, histone deacetylase inhibitors, and antibody drugs. However, high-risk MM cases that are refractory to novel drugs remain, and further optimization of chemotherapeutics is urgently needed.

We had achieved asymmetric total synthesis of komaroviquinone, which is a natural product from the plant *Dracocephalum komarovi*. Similar to several leading antitumor agents that have been developed from natural compounds, we describe the antitumor activity and cytotoxicity of komaroviquinone and related compounds in bone marrow cells. Our data suggested that komaroviquinone-related agents have potential as starting compounds for anticancer drug development.

Multiple myeloma (MM) is a neoplastic disease of immunoglobulin-producing plasma cells. Although <1% plasma cells are present in the bone marrow under normal conditions, various symptoms appear when plasma cells transform into cancer cells (myeloma cells), and numbers of myeloma cells reportedly increase in the bone marrow under these conditions.[1] Myeloma cells increase not only in the bone marrow but also in other organs and tumors that develop in other places are called plasmacytomas.

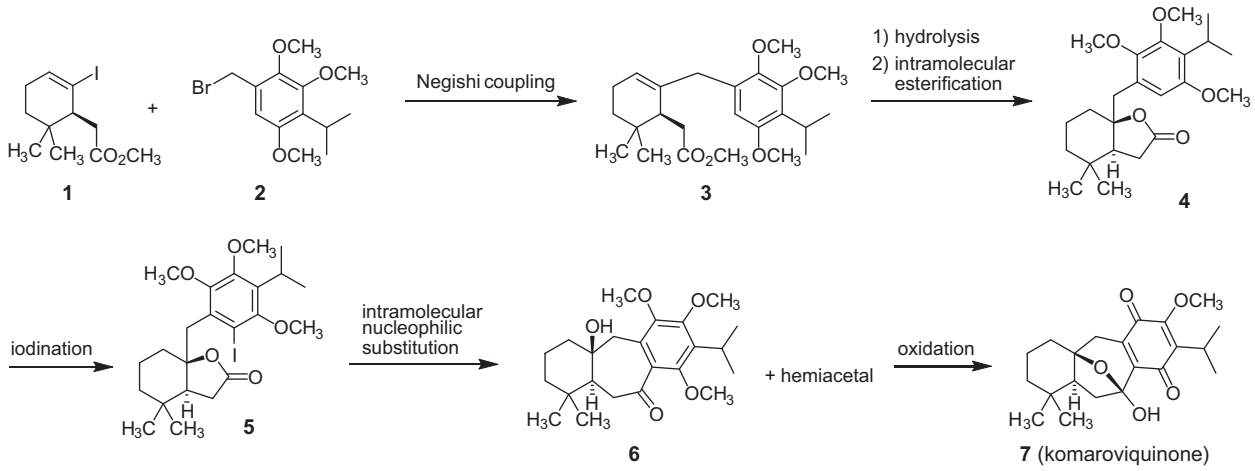
Myeloma cells produce large quantities of a monoclonal immunoglobulin (M-protein) that does not have normal functions. Under conditions of increased M-protein production, immunoglobulin secretions from normal plasma cells decrease and immune functions deteriorate, resulting in vulnerability to infections. In addition, obstruction of hematogenous functions of the bone marrow by myeloma cells induces feebleness, breathlessness, or anemia. Bone lytic lesions are typical among MM patients and manifest as pain, pathologic fracture, spinal cord compression, and hypercalcemia. Additionally, M-proteins damage organs such as the kidney and cause malfunction.[1]

Anticancer agents such as melphalan, vincristine, and doxorubicin are widely used to treat MM. In the 2000s, the proteasome inhibitor bortezomib was developed as a new class of drug for MM treatment, and thalidomide was reported to be effective against MM. Subsequently, the thalidomide derivative lenalidomide was developed and tested as a treatment for MM. Currently, these drugs are used in combination with conventional drugs as initial treatments for MM.[2] However, drugs such as bortezomib and lenalidomide fail to sufficiently improve prognoses of patients with high-risk MM.[3] New drugs are still developed presently and thalidomide derivative pomalidomide[4] and proteasome inhibitors, ixazomib[5] and carfilzomib,[6] were approved. In addition, histone deacetylase (HDAC) inhibitor, panobinostat,[7] and monoclonal antibodies, elotuzumab[8] and daratumumab,[9] have become available as drugs for MM with different mechanism. As described here, options for the treatment of MM have increased and prognoses of patients with MM have improved. However, MM remains incurable and further developments of more effective agents are urgently required for high-risk MM in particular.

Recently, we had developed asymmetric total synthesis of komaroviquinone (Scheme 1)[10] which was previously isolated from *Dracocephalum komarovi*.[11] Komaroviquinone was shown to have antitrypanosomal activity[12] and we determined the same

* Corresponding author.
E-mail address: ysuto@takasaki-u.ac.jp (Y. Suto).

http://dx.doi.org/10.1016/j.bmcl.2017.08.054
0960-894X/



Scheme 1. Asymmetric total synthesis of komaroviquinone.

activities for compounds with quinone moieties identical to those of komaroviquinone.[13] Although multiple antitumor agents have been developed from natural products,[14] the antitumor activities of komaroviquinone and its derivatives have not been reported. Komaroviquinone is also a diterpene and a previous study of antitumor activities warrants consideration of diterpenes as seed compounds for novel antitumor agents.[15] Accordingly, we screened komaroviquinone and related compounds using cytotoxicity assays in MUM24 cells,[16] which were derived from a high-risk MM patient who was refractory to thalidomide.

Initially, we tested cytotoxic activities of komaroviquinone in MUM24 cells cultured at 37 °C in the presence of 5% CO_2. In these experiments, komaroviquinone was added to culture media and cell death was determined after 48 h of incubation. Komaroviquinone showed cytotoxic activities against MUM24 cells at sub μM concentrations, with a half-inhibitory concentration (IC_{50}) value of 0.65 μM (Fig. 1). However, komaroviquinone also strongly inhibited the differentiation of normal bone marrow cells at 1 μM (Fig. 1). Because the ratios of CFU–MIX, CFU–GM, and BFU–E were almost the same regardless of compound concentrations, komaroviquinone might be cytotoxic and may not selectively inhibit the differentiation of bone marrow cells.

Reactive oxygen species (ROSs) are reportedly produced by *Trypanosoma cruzi* and could be related to the antitrypanocidal activities of komaroviquinone.[12b] It could be also speculated that komaroviquinone generated ROSs in MUM24 cells and they were involved in the cytotoxic activities[17] and we monitored cytotoxic activities of various compounds with quinone moieties identical to those of komaroviquinone. In these experiments, quinone compounds **8**–**15** all exhibited cytotoxic activities in MUM24 cell (Fig. 2) and compounds **12**–**15** was shown to have promising IC_{50} values. These compounds lack the three chiral carbon centers on the center and left side of komaroviquinone. Because these chiral centers make the synthesis of komaroviquinone difficult, simpler compounds, especially **14** and **15** are promising candidates for further optimization. Accordingly, although compounds **14** and **15** have a single chiral carbon center, their synthesis was sufficiently simple to allow studies of structure activity relationships (SAR) and we can investigate the effect of substituents on the phenyl ring and heterocycles.

Although compound **15** had promising cytotoxic activity against MUM24 cell, its toxicity in normal bone marrow cells was similar to that of komaroviquinone (Fig. 3), suggesting a relationship between the quinone structure and toxicity in bone marrow cells. Accordingly, the present quinone compounds exhibited cytotoxicity against MUM24 cells but are likely to be toxic to normal bone marrow cells.

Because the present data suggest that the quinone moiety participates in toxicity against normal bone marrow cells, we determined cytotoxic activities of komaroviquinone-related hydroquinone dimethyl ethers **4**, **6** (with hemiacetal)[18] and **16** (Fig. 4). Among these compounds, compound **4**, the intermediate

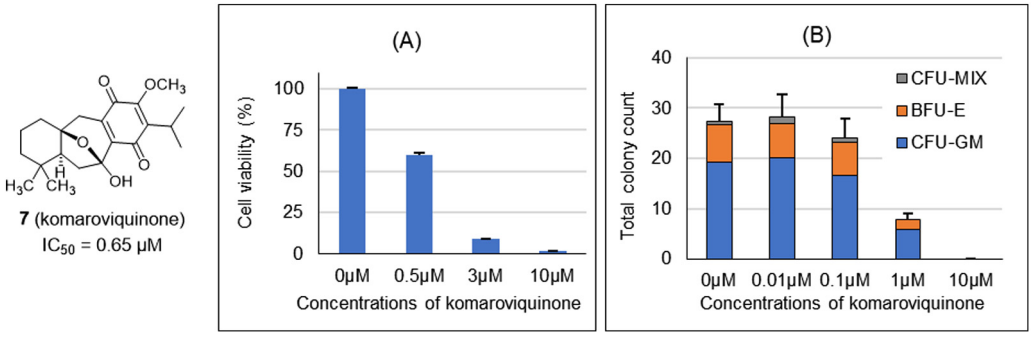


Fig. 1. (A) Cytotoxic activities of komaroviquinone in MUM24 cells; (B) toxicity of komaroviquinone in normal bone marrow cells; effects of komaroviquinone on the differentiation of normal bone marrow cells. CFU-MIX = Colony Forming Unit-mix. BFU-E = Burst Forming Unit-Erythroid. CFU-GM = Colony Forming Unit-Granulocyte Macrophage.